Aus der Klinik für Kardiologie und Pneumologie

(Prof. Dr. med. G. Hasenfuß)

der Medizinischen Fakultät der Universität Göttingen

Comparison of sarcopenia and cachexia in men with chronic heart failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

INAUGURAL-DISSERTATION

zur Erlangung des Doktorgrades

der Medizinischen Fakultät der

Georg-August-Universität zu Göttingen

vorgelegt von

Amir Emami

aus

Mashhad/Iran

Göttingen 2020

Dekan:	Prof. Dr. med. W. Brück
Referent/in	Prof. Dr. Dr. Stephan von Haehling
Ko-Referent/in:	Prof. Dr. Christoph Hermann-Lingen
Datum der mündlichen Prüfung:	18.05.2021

Dekan:	Prof. Dr. med. W. Brück

Betreuungsausschuss

Betreuer/in	Prof. Dr. Dr. Stephan von Haehling
Ko-Betreuer/in:	Prof. Dr. Christoph Herrmann-Lingen

Prüfungskommission

Referent/in	Prof. Dr. Dr. Stephan von Haehling
Ko-Referent/in:	Prof. Dr. Christoph Hermann-Lingen
Datum der mündlichen Prüfung:	18.05.2021

Hiermit erkläre ich, die Dissertation mit dem Titel "Comparison of sarcopenia and cachexia in men with chronic heart failure: Results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)" eigenständig angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Göttingen, den 30.11.20 ……

(Unterschrift)

Die Daten, auf denen die vorliegende Arbeit basiert, wurden teilweise publiziert:

Emami A, Saitoh M, Valentova M, Sandek A, Evertz R, Ebner N, Loncar G, Springer J, Doehner W, Lainscak M et al. (2018): Comparison of sarcopenia and cachexia in men with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). Eur J Heart Fail 20, 1580-1587

Table of Contents

List of figures

List of tables

List of abbreviations

6MWT	6-minute walk test
ACE-inhibitors	angiotensin-converting enzyme inhibitors
ANOVA	analysis of variance
ANCOVA	analysis of covariance
ASM	appendicular skeletal muscle mass
ASMI	appendicular skeletal muscle mass index
AT 1 antagonists	angiotensin II receptor type 1 antagonists
ATS	American Thoracic Society
BMI	body mass index
CAD	coronary artery disease
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
EF	ejection fraction
EQ-5D	EuroQOL 5-Dimensions
ESC	European Society of Cardiology
GFR	glomerular filtration rate
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR-QoL	health-related quality of life
IL-1β	interleukin-1β
IL-6	interleukin-6
JVP	jugular venous pressure
MRAs	mineralocorticoid receptor antagonists
NYHA	New York Heart Association
PeakVO_2	peak oxygen uptake
QOL	quality of life
SPPB	short physical performance battery
TNF	tumor necrosis factor
TTE	transthoracic echocardiogram

1 Introduction

1.1 Heart failure

Heart failure (HF) is present when the heart is incapable of providing necessary metabolic needs of body tissues (Tanai and Frantz 2015). The prevalence of HF is higher in the older population. About 6-10% of people aged > 65 years are considered to be affected by HF. The relative incidence of HF is lower in women. However, at least 50% of the HF cases are female due to the better life expectancy (Mann et al. 2018). Management of HF patients has a high financial burden for the healthcare system; for example, current US costs for HF are estimated at $30 billion per year (Heidenreich et al. 2013, Mazurek and Jessup 2017). Coronary artery disease (CAD) is a major HF cause in industrialized countries. Hypertension is well known to be responsible for 75% of HF cases, including most patients with CAD (Mann et al. 2018). Likely, diabetes mellitus intensifies the development of HF. The risk of HF multiplies when all CAD, hypertension, and diabetes co-exist (Mann et al. 2018). About 20-30% of cases of HF with reduced ejection fraction (HFrEF) remain idiopathic (Mann et al. 2018). These patients are referred to as non-ischemic or idiopathic cardiomyopathy. Other less common causes of HF include prior viral infection and toxin exposure. High cardiac output (e.g., arteriovenous fistula, anemia) could also lead to HF without any previously known structural heart disease. However, structural heart disease can develop into overt HF (Mann et al. 2018).

HF can be described as acute or chronic according to disease progress or onset. Compensated HF is present when a measurable dysfunction of cardiac pump function co-exists with predictable symptoms of HF, which include shortness of breath on exertion. Decompensated HF is present when these predictable symptoms of HF change and the situation worsens acutely (Schneider et al. 2018).

Left-sided HF is mostly a result of ventricular myocardial disorders such as cardiomyopathy or myocardial infarction. Likely, HF could emerge secondarily as a result of valvular heart disease or hypertension. Primary known causes of right HF are increased pulmonary vascular resistance (e.g., lung disease with cor pulmonale), right heart valvular disease, and shunt disease with volume overload. A decompensated left HF can secondarily develop into right HF or global HF as well.

HFrEF, previously known as systolic HF, is defined by marked dysfunction of cardiac contraction. However, HF with preserved ejection fraction (HFpEF), otherwise known as diastolic HF, results from dysfunctional cardiac filling. According to echocardiographic characteristics, HF patients with decreased ejection fraction (EF < 40%) and symptoms of HF are categorized as HFrEF (ESC 2016). The definition of HFpEF is a little bit more complicated. Symptomatic HF patients with EF ≥ 50% are called HFpEF when they show elevated natriuretic peptides and at least one of the following additional criteria: relevant structural heart disease or evidence of diastolic dysfunction (ESC 2016, Schneider et al. 2018). The New York Heart Association classification (NYHA) categorizes HF patients based on their exercise tolerance (Table 1, Mann et al. 2018). The NYHA classification is essential to validate particular therapy indications and inclusion in clinical trials (Januzzi et al. 2018).

Table 1. NYHA classification (Januzzi et al. 2018).

NYHA classification:	
I	No limitation in physical activity. Ordinary physical activity does not cause symptoms of HF.
II	Slight limitation in physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
III	Marked limitation in physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
VI	Unable to perform any physical activity without symptoms of HF or symptoms of HF at rest.

Worsening dyspnea is a major symptom of HF, and it is commonly the result of an increase in cardiac filling pressure or reduced cardiac output (Januzzi et al. 2018). HF patients may try to sleep in an upright position to decrease the dyspnea (orthopnea). Paroxysmal nocturnal dyspnea and Cheyne-Stokes respiration are frequently overlooked symptoms (Januzzi et al. 2018). Fatigue is a consequence of a reduction in cardiac output or abnormal metabolic responses of the skeletal muscle to exercise (Januzzi et al. 2018). Unintended weight loss, often leading to cachexia, is well known to have a prognostic value among HF patients (Anker et al. 1997, Januzzi et al. 2018).

Jugular venous pressure (JVP) is a reliable tool to evaluate volume retention. An elevated JVP has reasonable sensitivity (70%) and specificity (79%) for increased left-sided filling pressure (Januzzi et al. 2018). Pleural effusions commonly emerge bilaterally. However, unilateral pleural effusion resulting from HF usually presents on the right side (Januzzi et al. 2018). Lower extremity edema may result from volume retention or a side effect of pharmacologic therapy (e.g., calcium channel blockers, Januzzi et al. 2018).

HF is essentially a clinical diagnosis. However, several diagnostic tools are frequently used to ascertain the diagnosis. Two-dimensional echocardiography provides a semi-quantitative assessment of left ventricular size, function, or possible structural disorders. In this regard, EF is a crucial parameter to assess cardiac function. EF ≥ 50% usually reflects an adequate systolic function (Mann et al. 2018). Prominent reduced EF < 40% is assumed to be a sign of significantly impaired cardiac pump function (Mann et al. 2018).

Cardiopulmonary exercise testing (CPET) is a routine method for assessment of exercise capacity. Besides, CPET is applied to evaluate the prognosis or response to therapy (Mann et al. 2018). Furthermore, CPET could also serve as an initial diagnostic tool in the early stages of heart failure (Malhotra et al. 2016). A peak oxygen uptake (peakVO_2) < 14 mL/kg/min has been shown to correlate with poor prognosis (Anker et al. 1997, Mann et al. 2018). Specific cut-offs for peakVO_2 have been defined to assess eligibility for heart transplantation (Ramos-Barbón et al. 1999).

1.2 Co-morbidities of heart failure

Most discussed co-morbidities of HF such as chronic kidney disease (CKD, Schefold et al. 2015), diabetes mellitus (Kim et al. 2010), or chronic obstructive pulmonary disease (COPD, Lainscak et al. 2015) affect about 30-50% of HF patients (von Haehling 2017a). Other co-morbidities include hypertension, obesity, anemia, and atrial fibrillation (von Haehling 2017a). Sleep apnea is discussed as an independent risk factor of death in patients with HF (Javaheri et al. 2011). Muscle wasting, also known as sarcopenia, is primarily known as a geriatric disorder. However, similar loss in muscle mass and strength is observed among HF patients (von Haehling 2017a). A recent consensus suggests differentiating primary sarcopenia (i.e., a result of aging) from secondary sarcopenia. The secondary sarcopenia is discussed to be a consequence of advanced underlying disorders such as HF (Bauer et al. 2019). Iron deficiency has recently received tremendous attention (von Haehling 2017a). In the framework of CONFIRM-HF, Ponikowski et al. in 2015 showed a significant improvement in functional performance and quality of life (QOL) of HF patients with iron-

deficiency after one year of therapy with ferric carboxymaltose (FCM, Ponikowski et al. 2015).

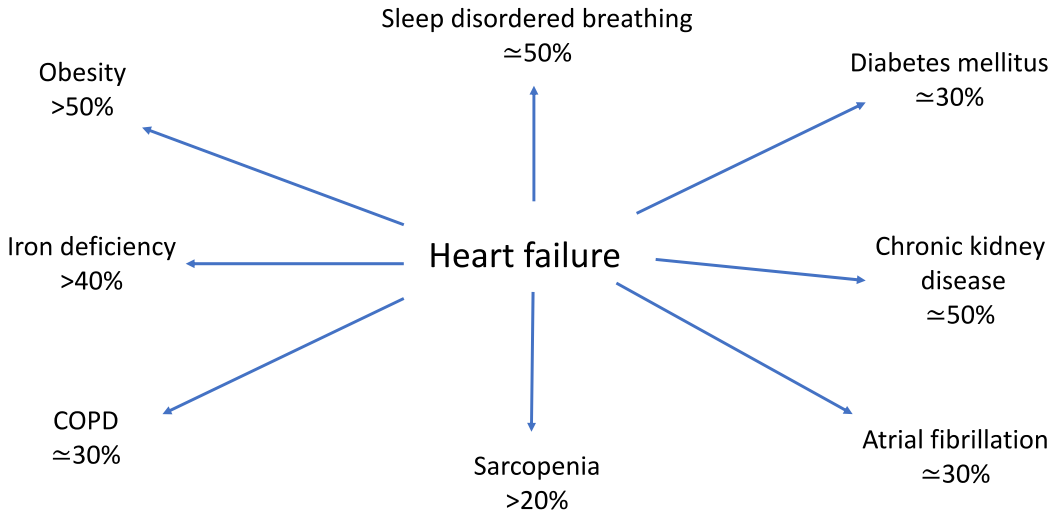


Figure 1. The estimated prevalence of some important co-morbidities in patients with HF (von Haehling 2017a). Usage with kind permission of the publisher (John Wiley and Sons).

1.3 Wasting in heart failure

The term wasting describes the loss of tissue independent of its type because adipose tissue, muscle, and bone can likewise be affected. The term "sarcopenia" from Greek "*sarx*" (flesh) and "*penia*" (loss), meaning poverty of flesh, was initially suggested in 1989 by Rosenberg to describe muscle changes that occur during healthy aging (von Haehling et al. 2017b, Rosenberg 2011). The annual loss of 1-2% of muscle mass has been discussed during the normal aging process (Abellan van Kan G 2009, von Haehling et al. 2017b). The term cachexia means "bad condition" (derived from the Greek "*kakós*" for bad and "*hexis*" for condition, von Haehling et al. 2017b). Many chronic diseases have been shown to result in significant weight loss (von Haehling et al. 2017b). A state of involuntary weight loss that cannot be reversed by changes in nutritional intake is described as cachexia (von Haehling et al. 2017b). Cachexia occurring in the process of HF is called cardiac cachexia (von Haehling et al. 2017b). Anker et al. (2003) showed weight loss ≥ 6% as the strongest predictor of death among HF patients. This cut-off showed the most prognostic value between other suggested percentages to define cardiac cachexia (Anker et al. 2003).

1.3.1 Pathophysiology of muscle wasting in heart failure

Reduced cardiac output and systemic congestion in chronic HF lead to reduced food intake and exercise capacity (Yin et al. 2019). Furthermore, it initiates the release of inflammatory factors, increases sympathetic excitability and secretion of muscle-related hormones (Yin et al. 2019). These parameters' interaction leads to a decline in skeletal muscle growth factors and an increase in oxidative damage. The oxidative stress induces the ubiquitin-proteasome system (UPS) activity and increases autophagy and apoptosis (Yin et al. 2019).

Skeletal muscle includes different fiber types. Slow-twitch type I fibers specialized for continuously extended muscle contractions use mainly aerobic metabolism. Fast-twitch type II fibers are responsible for quick contraction, which in contrast to type I fibers, usually uses anaerobic metabolism (von Haehling et al. 2017b). Aging leads to a cascade of changes that result in atrophy of type II fibers. These changes embrace alteration in neuromuscular junctions and peripheral motor neuron loss (von Haehling et al. 2017b).

Fatty tissue infiltration plays a pivotal role in the structural muscle changes in sarcopenia. Besides, oxidative damage leads to mitochondrial dysfunction and an anabolic-catabolic imbalance (von Haehling et al. 2017b). Tumor necrosis factor (TNF) is associated with increased myocyte apoptosis, which could accelerate the process of muscle loss among HF patients (Figure 2, von Haehling et al. 2017b). Altogether, muscle loss occurs earlier than fat depletion during the progress of the chronic disease, leading to earlier deprivation of exercise tolerance than weight loss (von Haehling et al. 2017b).

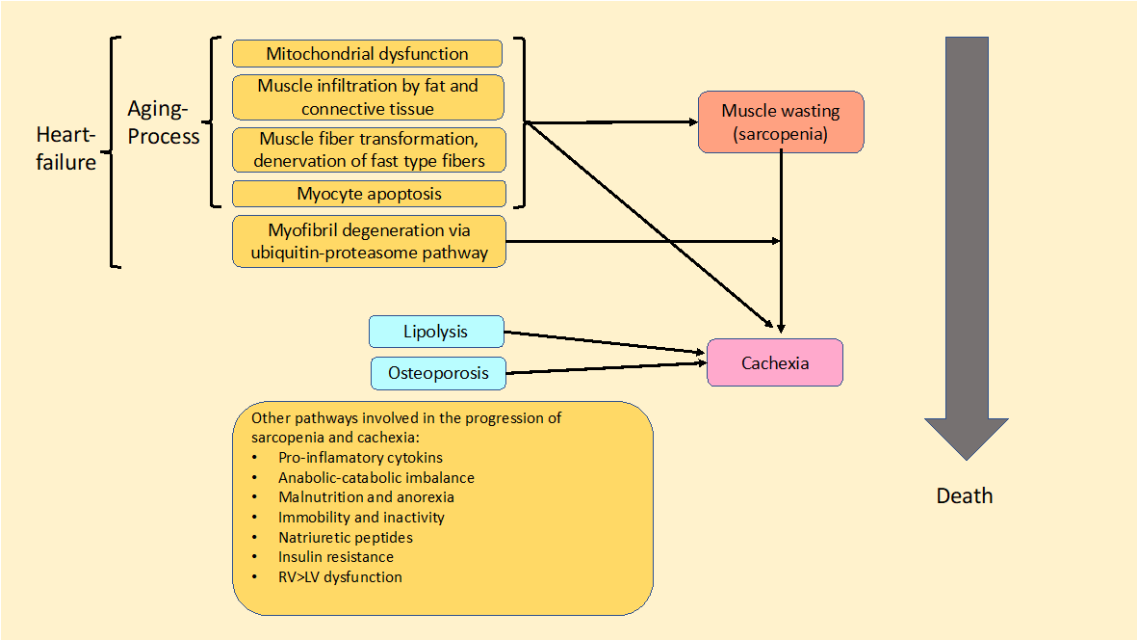


Figure 2. Wasting continuum in HF (von Haehling et al. 2017b). Usage with kind permission of the publisher (Springer Nature).

1.3.2 Treatment of wasting in HF

No specific pharmacological therapy has been approved for wasting in HF (ESC 2016). Potential treatments include anti-myostatin antibodies, ghrelin-receptor agonists such as anamorelin, anti-inflammatory substances, and proteasome inhibitors (Saitoh et al. 2017, von Haehling et al. 2017b, Ishida et al. 2019). Appetite stimulants, nutritional supplementation, exercise training, testosterone, and other anabolic stimulants are other possible therapies, which need more clinical and safety evaluation (ESC 2016).

Protein intake of 0.8 g/kg of body weight per day is recommended for HF patients (von Haehling et al. 2017b). However, in patients with muscle wasting, 1.0-1.2 g/kg of body weight per day might be indicated (von Haehling et al. 2017b, Payne-Emerson and Lennie 2008). Similarly, a calorie intake of up to 35 kcal per kg of body weight per day should be safe (Okoshi et al. 2013). Cardiac rehabilitation programs are shown to improve functional performance and QOL and reduce hospital admission and mortality rates (Piepoli et al. 2004, von Haehling et al. 2017b).

1.4 Measurement of muscle mass

The most common techniques to measure muscle mass include computed tomography (CT), magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA), and bioelectric impedance (BIA, Buckinx et al. 2018). In contrast to other methods, DXA is more accessible, has lower radiation exposure (< 1 μSv for whole-body scans), and costs less (Buckinx et al. 2018). These advantages make DXA the most practical approach in sarcopenia research at present (Buckinx et al. 2018). Due to higher costs, sectional imaging techniques like CT and MRI are less applicable in daily clinical practice or even for research purposes (Buckinx et al. 2018).

According to the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) working group on frailty and sarcopenia, DXA is the gold standard for the assessment of muscle mass (Buckinx et al. 2018). The measured lean mass with DXA is highly comparable with the results of MRI and CT (Bredella et al. 2010, Maden-Wilkinson et al. 2013, Buckinx et al. 2018). The sum of skeletal muscle mass and all other organs is called total body lean soft tissue mass (Buckinx et al. 2018). The muscle mass in the arms and legs, representing about 75% of total body skeletal muscle mass, is termed Appendicular skeletal muscle mass (ASM, Buckinx et al. 2018). Appendicular skeletal muscle mass index (ASMI) is calculated by ASM divided by the squared height in meters (Buckinx et al. 2018).

Clark RV et al. (2017), in a study among 14 older patients including 13 healthy subjects and one HF patient, showed a strong correlation between creatine (methyl-d3) dilution in urine and the muscle mass estimate by MRI. They also observed the highest correlations between MRI and DXA. However, they reported a greater magnitude of bias DXA than with the D3-creatine methods (Clark RV et al. 2017). Future studies with a greater number of patients are necessary to establish reliable laboratory screening tools for muscle wasting.

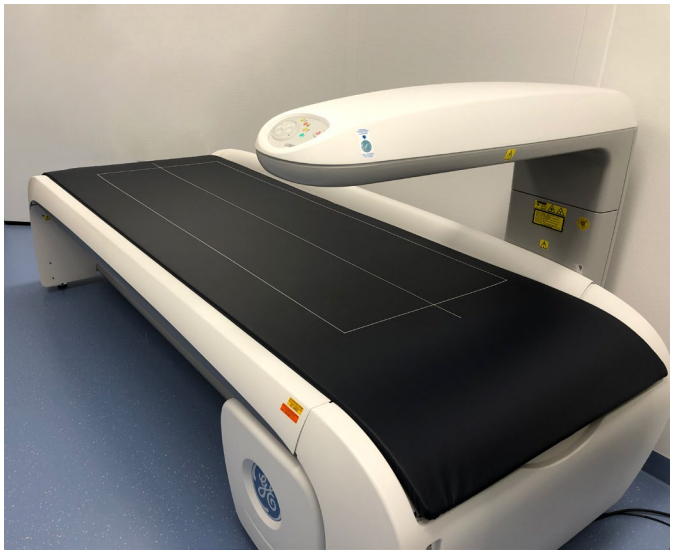


Figure 3. Lunar iDXA, GE Healthcare.

1.5 Assessment of functional capacity

The gold standard method for assessing functional capacity is the measurement of oxygen consumption (VO_2) during CPET (Kaminsky and Tuttle 2015). The maximal oxygen uptake or peakVO_2 is the main parameter (Kaminsky and Tuttle 2015). The Bruce protocol is the most frequently used method among different standardized treadmill protocols (Bruce et al. 1963).

Field tests like the 6-minute walk test (6MWT) are alternative methods for the assessment of exercise tolerance. Considerably, 6MWT does not accurately predict peakVO_2 (Lucas et al. 1999). Some reports have suggested that failure to achieve a certain distance, such as 300 m or 450 m on the 6MWT, has a prognostic value (Cahalin et al. 1996, Lewis et al. 2001). The American Thoracic Society (ATS) published a detailed guideline for performing a 6MWT, such as that it should be performed in a 30 m long hallway. However, the corridor's length and type (oval *vs.* back-and-forth) may interfere with the patient's performance (Kaminsky and Tuttle 2015).

The Short Physical Performance Battery (SPPB) consists of different functional measures, including the assessment of gait speed (4 m), strength (sit to stand), and balance (standing position). A composite score is formulated, in which higher scores demonstrate better functional performance (Kaminsky and Tuttle 2015).

1.5.1 Analyzing muscular function

Tests of muscular function are not well standardized in cardiology but have been extensively used in gerontology. The handgrip dynamometer is a practical method to evaluate muscular strength. Patients should squeeze the handle of the dynamometer as hard as they can for 3 seconds (Kaminsky and Tuttle 2015). After an initial examination, the test is repeated two more times, and the best of the three tests is used (Kaminsky and Tuttle 2015). Lower limb muscle strength measurements usually include measurement of quadriceps strength (Cruz-Jentoft et al. 2010). Similar to handgrip strength, quadriceps strength has a prognostic value in the elderly. Muscle strength is shown to correlate with exercise intolerance (Hairi et al. 2010, Rantanen et al. 1994; 2001, Visser et al. 2005), hospitalization (Cawthon et al. 2009), and mortality (Chan et al. 2014, Laukkanen et al. 1995, Newman et al. 2006).

1.6 Assessment of quality of life (QOL)

The negative impact of HF on health-related quality of life (HR-QoL) is well known (Juenger et al. 2002). Three main questionnaires have been validated to assess QOL in HF patients (Gallagher et al. 2019). Minnesota Living with Heart Failure Questionnaire (MLHFQ) includes 21 HF specific questions and analyzes HR-QoL during the last month. A higher score reflects a lower HR-QoL (Gallagher et al. 2019). The Kansas City Cardiomyopathy Questionnaire (KCCQ) consists of 23 specialized HF-related questions. It includes several aspects of patients' symptoms, self-efficacy, and physical and social limitations (Gallagher et al. 2019). A higher score is representative of a better QOL (Gallagher et al. 2019).

The EuroQoL-5-Dimensions (EQ-5D) questionnaire consists of two sections. The first part, known as "health score", includes assessing the patient's mobilization, self-care, pain/discomfort, and depression/anxiety levels (Gallagher et al. 2019). The second part is a visual analog index score from 0 to 100, which provides a quantitative self-measured reflection of the patients' health (Gallagher et al. 2019). The health score is converted to a country-specific index. A maximum health index score of 1 representing the perfect health status (Gallagher et al. 2019). The EQ-5D questionnaire is shown to have the highest total completion rate among all validated questionnaires (Gallagher et al. 2019).

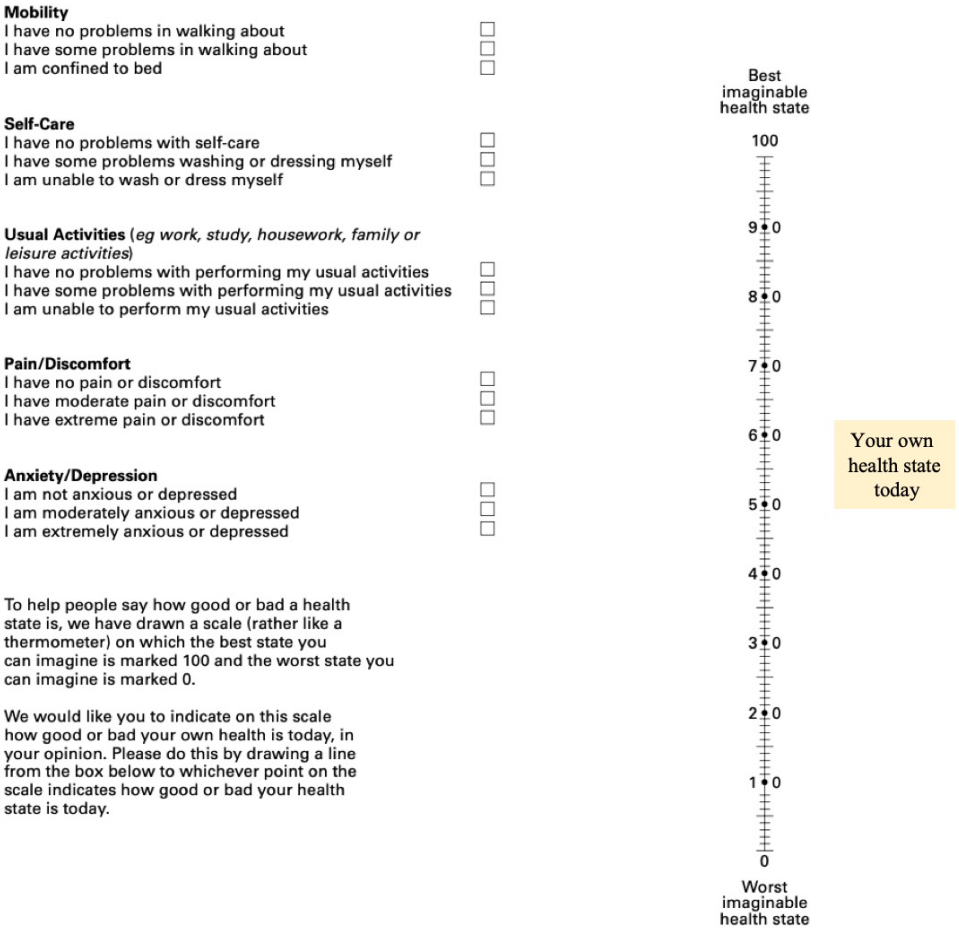


Figure 4. EQ-5D questionnaire (Schrag et al. 2000). Usage with kind permission of the publisher (BMJ).

1.7 Cachexia vs. sarcopenia

The prognostic importance of wasting is well established in other chronic diseases such as acquired immune deficiency syndrome (AIDS, Kotler et al. 1989) and cancer (Argilés et al. 2014). Anker et al. (1997) showed higher mortality rates among HF patients with cachexia and, likewise, in patients with a peakVo_2 < 14 mL/kg per min (Figure 5). Their study was the first to highlight the prognostic importance of cachexia and its functional influence on HF patients.

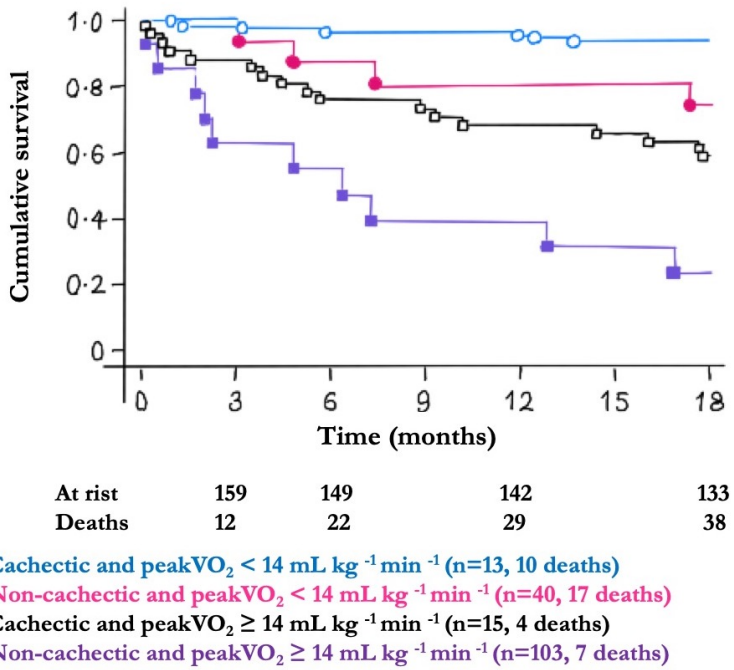


Figure 5. Kaplan-Meier survival and cumulative hazard curves for 18-month survival (Anker et al. 1997). Usage with kind permission of the publisher (Lancet).

Correspondingly, muscle wasting is known to decrease the functional capacity in both HFrEF and HFpEF patients (Fülster et al. 2013, Bekfani et al. 2016). In recently published data with prospectively enrolled ambulatory patients, muscle wasting was demonstrated as an independent predictor of death in chronic HF (Bielecka-Dabrowa et al. 2020). In 2017, Hajahmadi et al. demonstrated a shorter distance walked in 6MWT among patients with dilated cardiomyopathy (Hajahmadi et al. 2017).

In addition, cachexia requires underlying chronic illness such as HF, whereas sarcopenia may appear as part of the normal aging process (Cruz-Jentoft et al. 2010, Alchin 2014). It is essential to be aware of this issue because the age difference could affect the functional capacity. Severe obesity is known to have negative functional impacts. However, in established severe obesity, additional weight gain does not significantly limit the functional capacity any further (Pataky et al. 2014).

Sarcopenia is known to diminish not only exercise tolerance but also muscle strength in HF patients. Fülster et al. (2013) showed significantly lower peakVO_2, and distance walked in 6MWT among HF patients with sarcopenia.

Another crucial factor, which is usually missed in the routine assessment of HF patients is QOL. Muscle loss as a part of sarcopenia will lead to decreased muscle strength, which could indirectly harm the patient's QOL (Roubenoff et al. 1997).

1.8 Aims

The main goals of our study were as follows: To analyze body composition among patients with HF, to assess the prevalence of each type of wasting among HF patients, to investigate the overlap population (sarcopenia+cachexia) as an independent wasting category, and to compare the influence of different patterns of wasting on functional capacity, muscle strength, and QOL.

2 Materials and methods

2.1 Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

SICA-HF was a prospective, multinational, pathophysiological, and observational assessment of ambulatory HF patients (von Haehling et al. 2010). SICA-HF was funded by the European commission's Seventh Framework Program (FP7/2007-2013) under grant agreement no. 241558 (SICA-HF) and from the Russian Ministry of Science and Education within the FTP "R&D in priority fields of the S&T complex of Russia 2007-2012" under state contract number 02.527.11.0007 (von Haehling et al. 2010). The study was conducted under the Declaration of Helsinki principles and local/national regulations (von Haehling et al. 2010). National and local ethics committees reviewed and approved the study protocol (von Haehling et al. 2010). All patients signed a written informed consent before inclusion or participated in any study-related examination (von Haehling et al. 2010). The inclusion and exclusion criteria of the SICA-HF are summarized in Table 2.

Table 2. Inclusion and exclusion criteria for SICA-HF (von Haehling et al. 2010).

Inclusion criteria	Exclusion criteria

- Clinical diagnosis of HF.
- Objective evidence of cardiac dysfunction, as evidenced by at least one of the following:
  - Left ventricular EF ≤ 40%.
  - Left atrial dimension > 4.0 cm (or > 2.5 cm/m in height).
  - N-terminal pro B-type natriuretic peptide hormone (NT-proBNP) > 400 pg/ml (> 47.3 pmol/l) (or B-type natriuretic peptide hormone (BNP) > 150 pg/ml).
  - Age > 18 years.
- Willingness to provide informed consent .
	- Previous heart transplantation.
	- History of unstable angina, myocardial infarction, stroke, cardiovascular revascularization, or open abdominal surgery within six weeks before the planned baseline visit.
	- Known pregnancy.
	- Patients on hemodialysis at baseline.
	- Unable to understand and comply with protocol or give informed consent.

According to the national kidney foundation report (2002), patients with a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for more than three months were categorized as CKD.

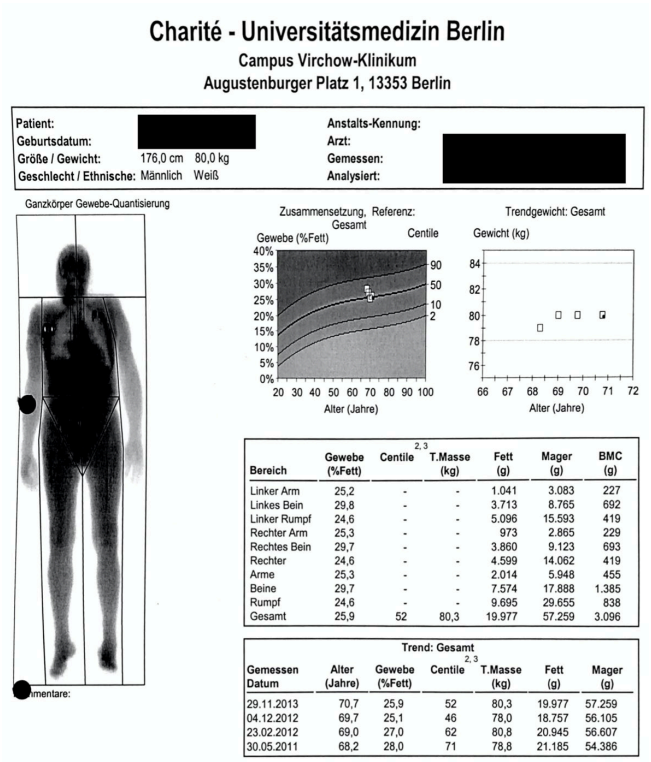
All patients underwent a transthoracic echocardiogram (TTE). The biplane Simpson method was used to calculate the left ventricular EF. In this technique, the left ventricular blood volume is measured in the end-diastole by tracings the blood-tissue interface in both apical four- and two-chamber views. Left ventricular length is also determined through a perpendicular line based on the middle of the mitral line at the cardiac apex. The EF of the left ventricle will be calculated automatically (Lang et al. 2015).

2.2 Study population

Overall, 207 ambulatory male patients with symptomatic HF with inclusion and exclusion criteria, as mentioned above, were enrolled in a prospective analysis. Both HFrEF and HFpEF patients were recruited into the study starting March 2010 until April 2012 at the Charité Universitäsmedizin, Berlin, Germany (Fülster et al. 2013). Being aware of the high prevalence of HFpEF among female patients, SICA-HF initially embraced 20.5% women. Due to the small prevalence of female patients, especially in the overlap group, we chose to exclude female patients solely for this analysis.

2.3 Body composition

The GE Lunar Prodigy DXA scanner was used to measure different parameters for body composition. The assessments were applied for total and individual body parts. The data analysis was performed with GE Lunar Encore software (Madison, WI, USA, Fülster et al. 2013), which automatically generates tables and diagrams with the possibility to compare the results with normal ranges for a particular age and gender. Regular controls and calibrations were performed according to the manufacturer's instructions. No metal objects like mobile phones, watches, or jewelry were allowed during the examination. As demonstrated in Figure 3, the patients had to lie on their back on the device surface. The scanner moves slowly over the patient's body. The scan time was usually about 15-20 minutes. Both fat mass and lean mass were reported as total and for particular body parts.



Charité - Universitätsmedizin Berlin
Campus Virchow-Klinikum
Augustenburger Platz 1, 13353 Berlin

Patient: [redacted]
Geburtsdatum:
Größe / Gewicht: 176,0 cm 80,0 kg
Geschlecht / Ethnische: Männlich Weiß
Anstalts-Kennung:
Arzt:
Gemessen:
Analysiert:

Ganzkörper Gewebe-Quantisierung

Zusammensetzung, Referenz: Gesamt
Gewebe (%Fett) Centile
40% 35% 30% 25% 20% 15% 10% 5% 0%
90 50 10 2
20 30 40 50 60 70 80 90 100
Alter (Jahre)

Trendgewicht: Gesamt
Gewicht (kg)
84 82 80 78 76
66 67 68 69 70 71 72
Alter (Jahre)

Bereich	Gewebe (%Fett)	Centile [2, 3]	T.Masse (kg)	Fett (g)	Mager (g)	BMC (g)
Linker Arm	25,2	-	-	1.041	3.083	227
Linkes Bein	29,8	-	-	3.713	8.765	692
Linker Rumpf	24,6	-	-	5.096	15.593	419
Rechter Arm	25,3	-	-	973	2.865	229
Rechtes Bein	29,7	-	-	3.860	9.123	693
Rechter	24,6	-	-	4.599	14.062	419
Arme	25,3	-	-	2.014	5.948	455
Beine	29,7	-	-	7.574	17.888	1.385
Rumpf	24,6	-	-	9.695	29.655	838
Gesamt	25,9	52	80,3	19.977	57.259	3.096

Trend: Gesamt

Gemessen Datum	Alter (Jahre)	Gewebe (%Fett)	Centile [2, 3]	T.Masse (kg)	Fett (g)	Mager (g)
29.11.2013	70,7	25,9	52	80,3	19.977	57.259
04.12.2012	69,7	25,1	46	78,0	18.757	56.105
23.02.2012	69,0	27,0	62	80,8	20.945	56.607
30.05.2011	68,2	28,0	71	78,8	21.185	54.386

Kommentare:

Figure 6. An example of a DXA result from SICA-HF.

2.4 Functional capacity and quality of life

An isokinetic dynamometer (Multitrace 2, Lectromed, Jersey, Channel Islands) was used to assess quadriceps strength (Fülster et al. 2013). The maximal strength was measured in a sitting position with both legs hanging freely as the ankle stabilized by a pressure transducer. The best of the three measurements was reported (Fülster et al. 2013). The handgrip strength was evaluated using a handgrip dynamometer (Saehan Corporation Korea Hydraulic Hand Dynamometer, model SH5001, Fülster et al. 2013), the highest measured value was reported respectively (Fülster et al. 2013). The Bruce protocol was used to perform CPET on a treadmill (Bruce et al. 1963). Ventilation parameters such as peakVO_2 (mL/min), anaerobic threshold, and carbon dioxide production (VCO_2 in mL) were measured (Fülster et al. 2013). Due to independence from the voluntary effort and substantial prognostic value, peakVO_2 and ventilatory patterns play a crucial role in estimating functional capacity (Fülster et al. 2013, Malhotra et al. 2016).

The 6MWT was performed according to the official statement of the American Thoracic Society (ATS pulmonary function 2002). The SPPB-test was performed using three subtests, including the standing balance test, walking speed test, and the sit-to-stand test. A maximum of 12 points demonstrates the best possible functional performance (Guralnik et al. 1994, Fülster et al. 2013).

Patients were asked to fill out the EQ-5D questionnaire. This questionnaire was used to calculate the EQ-5D index score.

2.5 Definitions and grouping

According to previously published international consensus, sarcopenia was defined as muscle mass two standard deviations (SD) below the mean of a healthy young reference group 18-40 years old (ASMI < 7.26 kg in men, < 5.45 kg in women, Morley et al. 2011, Gallagher et al. 1997).

Between the different cut-offs for cachexia, we chose a non-edematous, non-intentional weight loss ≥ 6% over at least one year as our main cut-off for cachexia because it had the highest prognostic value as compared to other possible choices (Anker et al. 2003).

Patients who fulfilled the criteria for sarcopenia but without associated cachexia were labeled as "sarcopenic HF". Patients with cachexia without a significant muscle loss were named as "cachectic HF". Also, patients with characteristics of both sarcopenia and cachexia were labeled as "overlap group". Finally, HF patients without sarcopenia or cachexia were included as the "control group".

2.6 Statistical analysis

Statistical Package for the Social Sciences (SPSS Statistics for Windows, Version 24.0, IBM Corp. Armonk, NY, USA) applied to analyze the results. Analysis of variance (ANOVA) was used to compare the basic characteristics of our four included groups. The analysis of covariance (ANCOVA) with Tukey's post hoc test was implemented to compare the functional capability, muscle strength, and QOL. Being aware of the possible interference of other limiting factors on functional parameters, we checked the assumption of homogeneity of regression slopes for all variables measured at baseline. Only age, BMI, and NYHA-classification have met this assumption. Functional parameters, muscle strength, and QOL were adjusted for the mentioned covariates, which met the ANCOVA's assumption. The results with a two-tailed p-value < 0.05 were interpreted as statistically significant.

3 Results

3.1 Clinical Characteristics

We prospectively enrolled 207 male outpatients with chronic HF. A total of 154 (74.4%) patients presented with HFrEF and 53 (25.6%) with HFpEF. The mean age of the participants was 67.3±10.1 years. TTE showed an average EF of 36.9±12.5%. No patient with NYHA classification IV was recruited; most of the included patients had NYHA classification II-III. The average measured BMI was 28.8±5.0 kg/m^2. Ischemic HF was determined in 59.9% of patients and atrial fibrillation in 39.1%. In addition, 38.2% of the participants had diabetes. Among our HF patients, 38.6% had CKD, but the patients with ongoing hemodialysis at baseline were excluded. Hypertension was determined in 59.4% and hyperlipidemia in 51.7% of our study population. The prevalence of anemia among our patients was 32.4%, whereas the hemoglobin level was significantly lower in the overlap group *vs.* the control group.

The sarcopenic HF group, as expected, had the highest age *vs.* cachectic HF and the control group ($p < 0.05$, Table 3). Furthermore, the overlap group showed the lowest BMI *vs.* the cachectic HF and the control group ($p < 0.05$, Table 3).

Among the measured inflammatory parameters, only the overlap group showed significantly lower results in IL-6 *vs.* the control group (without wasting, $p < 0.05$, Table 3). However, no significant differences were determined in IL-1 and TNF results.

Considering medication, 95.2% of participants were treated with Angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor type 1 antagonists (AT 1 antagonists) and 91.3% with beta-blockers, respectively. Furthermore, 59.9% were treated with thiazide or loop diuretics and 21.3% with Mineralocorticoid Receptor Antagonists (MRAs). Considerably, no significant difference was observed in pharmacological therapy among the four groups (Table 3).

Table 3. Baseline characteristics. ACE-inhibitors: Angiotensin-converting enzyme inhibitors, AT1-antagonists: angiotensin II receptor type 1 antagonists, BMI: body mass index, CKD: chronic kidney disease, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, hsCRP: high-sensitivity C-reactive protein, IL-1: interleukin-1, IL-6: interleukin-6, EF: ejection fraction, MRA: Mineralocorticoid Receptor Antagonists, NYHA: New York Heart Association classification, TNF: tumor necrosis factor. §: *vs.* control group, †: *vs.* sarcopenic HF group, *: *vs.* cachectic HF group. Each symbol denotes $p < 0.05$. Symbols in brackets denote a trend with $p < 0.1$. The inflammatory parameters such as TNF, interleukin-1β (IL-1β), or interleukin-6 (IL-6) were reported as the median and interquartile range (Emami et al. 2018). Usage with kind permission of the publisher (John Wiley and Sons).

	All (n = 207)	**Control (n = 138)**	**Cachectic HF (n = 25)**	**Sarcopenic HF (n = 30)**	**Overlap (n = 14)**	***p*-value**
Age (years)	67.3 ± 10.1	66.4 ± 10.8	64.3 ± 13.4	73.1 ± 8.4 § *	69.9 ± 9.3	0.008
NYHA classification (mean)	2.3 ± 0.6	2.2 ± 0.6	2.2 ± 0.6	2.4 ± 0.7	2.6 ± 0.6	0.09
BMI (kg/m²)	28.8 ± 5.0	30.1 ± 4.8	28.7 ± 4.3	25.7 ± 4.4 §	24.0 ± 3.6 § *	< 0.001
Weight change during the past 12 months (kg)	-0.2 ± 7.3	+2.0 ± 6.5	-9.5 ± 6.4 § †	+0.8 ± 2.9	-7.6 ± 4.2 § †	< 0.001
EF (%)	36.9 ± 12.5	38.7 ± 12.8	31.2 ± 9.7 §	36.7 ± 12.4	28.5 ± 7.2 §	0.002
HFrEF/HFpEF (%)	74.4/25.6	68.8/31.2	92.0/8.0	73.3/26.7	100/0	0.09
Ischaemic HF (%)	59.9	56.5	52.0	70.0	85.7	0.3
Hypertension (%)	59.4	58.7	72.0	46.7	71.4	0.009
Hyperlipidemia (%)	51.7	50.0	52.0	56.7	57.1	0.5

	All (n = 207)	Control (n = 138)	Cachectic HF (n = 25)	Sarcopenic HF (n = 30)	Overlap (n = 14)	*p*-value
Diabetes (%)	38.2	40.6	36.0	36.7	21.4	0.6
CKD (%)	38.6	37.0	44.0	43.3	35.7	0.8
Anemia (%)	32.4	25.4	40.0	50.0	50.0	0.02
Atrial fibrillation (%)	39.1	37.7	40	36.7	57.1	0.8
Mild peripheral edema (%)	57.0	60.1	56.0	53.3	35.7	0.2
hsCRP (mg/dL)	3.0 ± 2.3	2.8 ± 2.1	3.2 ± 2.6	3.4 ± 2.6	3.6 ± 2.0	0.6
IL-1 (pg/mL)	0.01 (0.01 - 0.08)	0.01 (0.01 - 0.07)	0.01 (00.01 - 0.07)	0.03 (0.01 - 0.1)	0.01 (0.01 - 0.1)	0.8
IL-6 (pg/mL)	1.2 (0.3 - 2.9)	1.0 (0.09 - 2.1)	1.2 (0.3 - 2.9)	1.8 (0.8 - 4.0) (§)	3.7 (1.6 - 6.1) §	0.01
TNF (pg/mL)	0.06 (0.06 - 1.9)	0.06 (0.06 - 1.8)	0.06 (0.06 - 1.9)	1.0 (0.06 - 2.9)	0.2 (0.06 - 2.9)	0.8
Creatinine (mg/dL)	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.6	1.2 ± 0.5	1.3 ± 0.4	0.8
Hemoglobin (g/dL)	13.6 ± 1.5	13.7 ± 1.5	13.5 ± 1.8	13.3 ± 1.3	12.6 ± 1.4 §	0.02
Albumin (mg/dL)	36.9 ± 12.5	37.7 ± 3.6	37.6 ± 4.1	36.1 ± 4.1	35.2 ± 3.5	0.06
Aspirin (%)	71.5	73.2	72.0	66.7	64.3	0.8

	All (n = 207)	Control (n = 138)	Cachectic HF (n = 25)	Sarcopenic HF (n = 30)	Overlap (n = 14)	*p*-value
ACE-inhibitors or AT_1-antagonists (%)	95.2	95.7	96.0	93.3	92.9	0.9
Beta-blocker (%)	91.3	90.6	88.0	96.7	92.9	0.6
Thiazide/Loop diuretics (%)	59.9	60.9	72.0	43.3	64.3	0.2
MRAs (%)	21.3	22.5	16.0	16.7	28.6	0.7

Sarcopenia without concomitant cachexia was present in 14.5% (sarcopenic HF group). Isolated cachexia without associated sarcopenia was observed in 12.1% (cachectic HF group). In addition, 6.7% showed the characteristics of both sarcopenia and cachexia (overlap group). Overall, 21.3% presented with sarcopenia (sarcopenic HF and overlap group) and 18.8% with cachexia (cachectic HF and overlap group, Figure 7).

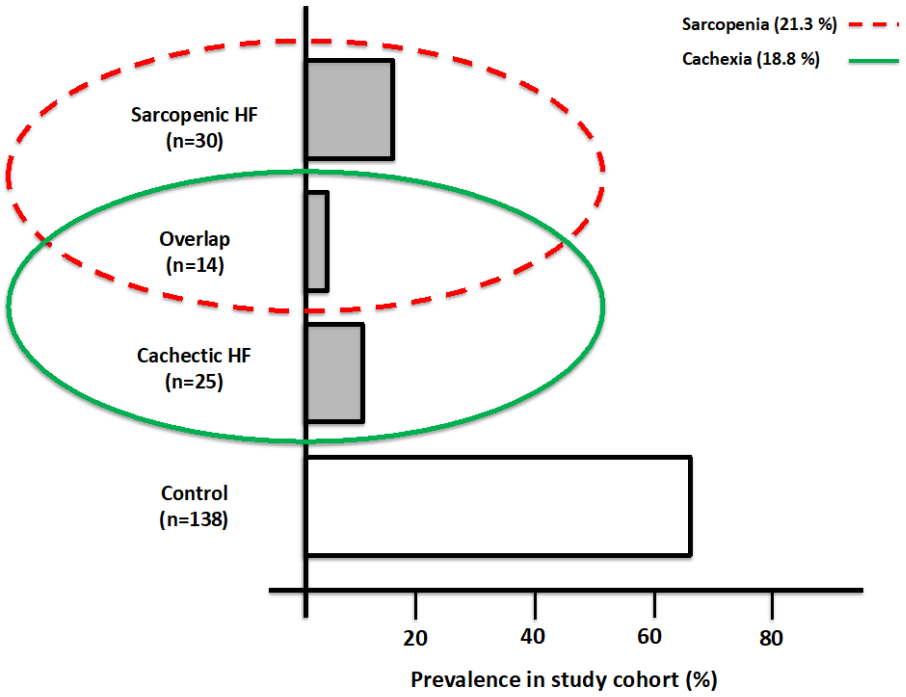


Figure 7. Prevalence of sarcopenia, cachexia, and their overlap. The prevalence of sarcopenia and cachexia in our study was 21.3% and 18%, respectively (Emami et al. 2018). Usage with kind permission of the publisher (John Wiley and Sons).

3.2 Functional capacity, muscle strength & QOL

The lowest results for functional capacity, muscle strength, and QOL were observed in the patients with sarcopenia *vs.* the control group without wasting. To be more exact, the overlap group showed the lowest values for handgrip strength, 6MWT, peakVO_2, and SPPB test *vs.* the control group ($p < 0.05$, Table 4 & Figure 8). Likely, the overlap group had lower EQ-5D index scores *vs.* the control group ($p < 0.05$, Table 4). In addition, the weakest quadriceps strength were observed in the overlap group ($p < 0.05$, Table 4 & Figure 8).

The sarcopenic HF was observed to have significantly lower results for muscle strength, distance walked in 6MWT, peakVO_2, SPPB score, and QOL index score *vs.* the control group ($p < 0.05$, Table 4 & Figure 8). Both the sarcopenic HF and overlap groups indicated shorter distance walked in 6MWT *vs.* the control group, but this effect was more prominent in the sarcopenic HF group ($p < 0.01$ *vs.* $p < 0.05$).

All three sarcopenic HF, cachectic HF, and overlap groups, showed significantly lower quadriceps strength and peakVO_2 *vs.* the control group. However, the most significant lower results were observed among the overlap group ($p < 0.001$). Both the functional and the

QOL analyses were adjusted for age, BMI, and NYHA classification, as these were the only significant parameters.

Table 4. Functional capacity, muscle strength, and QOL. 6MWT: 6-minute walk test, EQ-5D: EuroQol-5 Dimensions, HF: heart failure, peakVO_2: peak oxygen uptake, SPPB: Short Physical Performance Battery. Functional performance, muscle strength & QOL results are adjusted for age, BMI, and NYHA classification. §: *vs.* control group; †: *vs.* sarcopenic HF group, *: *vs.* cachectic HF group. Each symbol represents $p < 0.05$. Symbols in brackets indicate a trend with $p < 0.1$ (Emami et al. 2018). Usage with kind permission of the publisher (John Wiley and Sons).

	all **n=207**	**Control** **n=138**	**Cachectic HF** **n=25**	**Sarcopenic HF** **n=30**	**Overlap** **n=14**	***p*-value**
Handgrip strength (kg)	39.8 ± 11.2	41.8 ± 10.5	42.1 ± 13.8	33.2 ± 8.5 §	31.9 ± 10.5 § (*)	0.02
Quadriceps strength (kg)	39.9 ± 13.3	43.2 ± 12.7	38.7 ± 14.4 §	34.1 ± 10.5 §	24.7 ± 6.6 § * †	0.001
6MWT (m)	438 ± 136	455 ± 129	444 ± 88	362 ± 138 §	358 ± 136 §	0.02
PeakVO_2 (mL/min/kg)	17.7 ± 4.9	18.8 ± 4.7	16.5 ± 4.7 §	15.3 ± 4.3 §	12.7 ± 4.2 § (*) (†)	< 0.001
SPPB score	10.5 ± 2.0	10.8 ± 1.7	10.7 ± 1.6	9.5 ± 2.6 §	9.0 ± 2.8 § (*)	0.02
EQ-5D index score	0.89 ± 0.09	0.90 ± 0.09	0.91 ± 0.09	0.82 ± 0.07 § *	0.84 ± 0.1 § (*)	0.02

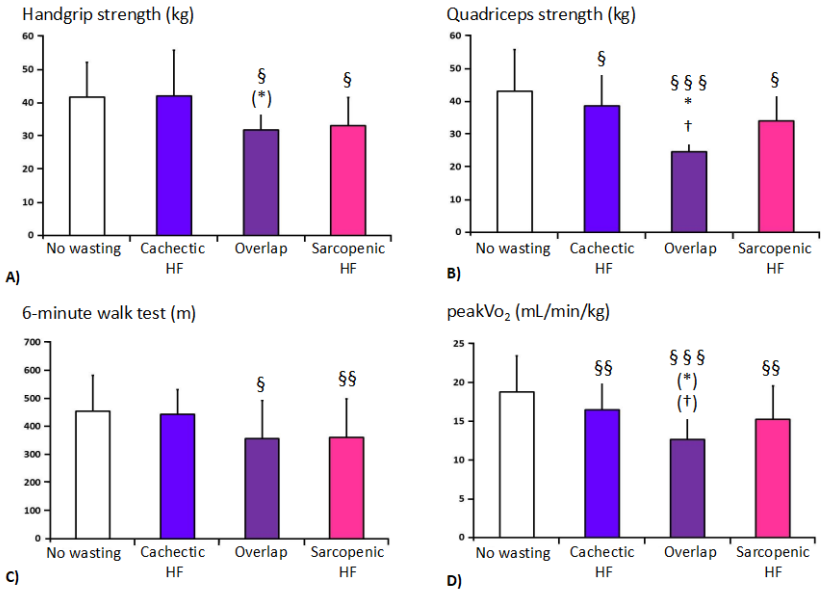


Figure 8. Functional capacity & muscle strength. (A) Handgrip strength, (B) Quadriceps strength, (C) 6-minute walk test, and (D) Peak oxygen uptake(peakVO_2) in the four study groups. HF: Heart failure. §: *vs.* control group, †: *vs.* sarcopenic HF group, *: *vs.* cachectic HF group. One symbol represents $p < 0.05$, two symbols $p < 0.01$, three symbols $p < 0.001$. Symbols in brackets indicate a trend with $p < 0.1$ (Emami et al. 2018). Usage with kind permission of the publisher (John Wiley and Sons).

3.3 Body composition

As compared to the control group, the overlap group showed significantly lower results for total, arms, and legs fat mass ($p < 0.05$ for all measures). In addition, the overlap group demonstrated lower truncal fat mass *vs.* all other groups ($p < 0.05$, Table 5). The total fat mass was also significantly lower in the overlap group *vs.* the sarcopenic HF group ($p < 0.05$, Table 5).

As expected, the sarcopenic HF group showed a lower lean mass in total and in other measured body parts *vs.* both cachectic HF and control group ($p < 0.05$, Table 5). The overlap group demonstrated similar impacts on most measurements except for truncal lean mass. ASM, as measured by the sum of lean muscle mass results of both arms and legs, was significantly lower in both sarcopenic HF and overlap groups ($p < 0.05$, Table 5).

Table 5. Body composition. ASM: appendicular skeletal muscle mass, ASMI: appendicular skeletal muscle mass index, HF: heart failure. §: *vs.* control group, †: *vs.* sarcopenic HF group, *: *vs.* cachectic HF group. Each symbol indicates $p < 0.05$. Symbols in brackets represent a trend with $p < 0.1$ (Emami et al. 2018). Usage with kind permission of the publisher (John Wiley and Sons).

	all (n = 207)	**Control** (n = 138)	**Cachectic HF** (n = 25)	**Sarcopenic HF** (n = 30)	**Overlap** (n = 14)	***p*-value**
Fat (kg)						
- arms	2.3 ± 0.9	2.4 ± 0.9	2.1 ± 0.8	2.0 ± 0.8 (§)	1.6 ± 0.9 §	0.001
- legs	7.6 ± 3.0	7.9 ± 2.9	6.7 ± 2.3	7.5 ± 3.5	5.4 ± 2.1 §	0.01
- trunk	16.8 ± 6.1	18.0 ± 5.5	15.7 ± 5.9	15.5 ± 7 .0	10.2 ± 4.5 § * †	< 0.001
- total	27.4 ± 9.7	29.1 ± 9.0	24.8 ± 9.1	25.9 ± 11.1	16.8 ± 7.3 § † (*)	< 0.001
Lean mass (kg)						
- arms	6.3 ± 1.1	6.5 ± 0.9	6.7 ± 1.0	5.4 ± 0.8 § *	4.9 ± 0.5 § *	< 0.001
- leg	18.9 ± 3.1	19.7 ± 2.7	19.9 ± 2.7	15.9 ± 1.9 § *	15.3 ± 2.2 § *	< 0.001
- trunk	28.5 ± 5.1	29.2 ± 5.1	29.7 ± 4.3	25.7 ± 4.9 § *	26.7 ± 3.4	0.001
- total	57.9 ± 8.5	59.0 ± 8.1	60.6 ± 7.6	51.0 ± 6.8 § *	50.2 ± 5.4 § *	< 0.001
ASM (kg)	24.9 ± 3.9	25.9 ± 3.4	26.1 ± 3.4	20.9 ± 2.4 § *	19.8 ± 2.8 § *	< 0.001
ASMI	8.0 ± 1.1	8.4 ± 0.8	8.5 ± 0.8	6.8 ± 0.5 § *	6.5 ± 0.6 § *	< 0.001

3.4 Alternative analyses

The overlap group embraces both the characteristics of sarcopenia and cachexia. It showed promising results in our functional capacity and QOL measurements. To reach a more comprehensive understanding of this group, we designed two alternative analyses.

The overlap group was joined in the first alternative grouping into the cachectic HF group to shape a combined "cachexia group". The other two groups remained unchanged. The new cachexia group showed significantly lower results *vs.* the control group for quadriceps strength and peakVO_2 ($p < 0.05$, Table 6) but could not demonstrate a significant difference in QOL indices. Similar to the primary analysis, the sarcopenic HF patients showed lower results for functional capacity and QOL *vs.* the control group (all $p < 0.05$, Table 6).

Table 6. First alternative analysis. The overlap group was included in the cachexic HF group as a combined "cachexia group". EQ-5D: EuroQol-5 Dimensions, HF: heart failure, 6MWT: 6-minute walk test, SPPB: Short Physical Performance Battery, peakVO_2: peak oxygen uptake. Functional performance, muscle strength & QOL models were adjusted for age, BMI, and NYHA classification. §: *vs.* control group, *: *vs.* cachexia group. Each symbol indicates $p < 0.05$. Symbols in brackets represent a trend with $p < 0.1$ (Emami et al. 2018). Usage with kind permission of the publisher (John Wiley and Sons).

	all (n = 207)	**Control (n = 138)**	**cachexia (n = 39)**	**sarcopenic HF (n = 30)**	***p*-value**
Handgrip strength (kg)	39.8 ± 11.2	41.8 ± 10.5	38.1 ± 13.4	33.2 ± 8.5 §	0.04
Quadriceps strength (kg)	39.9 ± 13.3	43.2 ± 12.7	33.7 ± 13.9 §	34.1 ± 10.5 (§)	0.002
6MWT (m)	438 ± 136	455 ± 129	410 ± 115 (§)	362 ± 138 §	0.02
PeakVO_2 (mL/min/kg)	17.7 ± 4.9	18.8 ± 4.7	15.0 ± 1.1 §	15.3 ± 4.3 §	< 0.001
SPPB score	10.5 ± 2.0	10.8 ± 1.7	10.0 ± 2.3 (§)	9.4 ± 2.6 §	0.03
EQ-5D index score	0.89 ± 0.09	0.90 ± 0.09	0.88 ± 0.09	0.82 ± 0.07 § (*)	0.04

We included the overlap group in the second optional analysis into the sarcopenic HF group to shape the "muscle wasting group". The other two groups, including cachectic HF and control groups, remained unchanged. As compared to the control group, all of the functional parameters, including peakVO_2, 6MWT distance, SPPB score, and muscle strength, were significantly lower in the muscle wasting group. Considerably, the muscle wasting group presented with a lower QOL *vs.* both other groups ($p < 0.05$ for all, Table 7).

It has to be kept in mind that none of the cachectic groups, including the unified cachexia group in the first analysis and the cachexic HF group in the second analysis, could demonstrate any significant impact on QOL indices. This effect was only observed among groups with sarcopenia. Furthermore, lower SPPB scores were only observed among sarcopenic patients *vs.* the control group.

Table 7. Second alternative analysis. The overlap group was included in the sarcopenic HF group to shape a unified "muscle wasting group". EQ-5D: EuroQol-5 Dimensions, HF: heart failure, 6MWT: 6-minute walk test, SPPB: Short Physical Performance Battery, peakVO_2: peak oxygen uptake. All functional and QOL models were adjusted for BMI, age, and NYHA classification. §: *vs.* control group, *: *vs.* cachectic HF group. Each symbol indicates $p < 0.05$. Symbols in brackets represent a trend with $p < 0.1$ (Emami et al. 2018). Usage with kind permission of the publisher (John Wiley and Sons).

	all **(n = 207)**	**Control** **(n = 138)**	**cachectic HF** **(n = 25)**	**muscle wasting** **(n = 44)**	***p*-value**
Handgrip strength (kg)	39.8 ± 11.2	41.8 ± 10.5	42.1 ± 13.8	32.8 ± 9.1 § (*)	0.009
Quadriceps strength (kg)	39.9 ± 13.3	43.2 ± 12.7	38.7 ± 14.4 (§)	31.1 ± 10.4 §	0.002
6MWT (m)	438 ± 136	455 ± 129	444 ± 88	360 ± 135 §	0.007
PeakVO_2 (mL/min/kg)	17.7 ± 4.9	18.8 ± 4.7	16.5 ± 4.7 §	14.4 ± 4.4 §	< 0.001
SPPB score	10.5 ± 2.0	10.8 ± 1.7	10.7 ± 1.6	9.3 ± 2.6 § (*)	0.009
EQ-5D	0.89 ± 0.09	0.90 ± 0.09	0.91 ± 0.09	0.83 ± 0.09 § *	0.04

4 Discussion

This is the first study to compare different types of body wasting in patients with HF. In a cross-sectional analysis in the framework of SICA-HF, we found sarcopenia in 21.3% of our HF patients. In this context, 14.5% fulfilled sarcopenia's definition without associated cachexia (sarcopenic HF group). 12.1% presented with cachexia without concomitant sarcopenia (cachectic HF group). Furthermore, 6.8% of patients demonstrated the characteristics of both sarcopenia and cachexia, denoted as the overlap group.

HF patients with sarcopenia had significantly lower muscle strength, functional capabilities, and QOL. Meanwhile, the overlap group had the weakest results *vs.* the control group. This effect was absent among other groups without sarcopenia.

HF patients with sarcopenia indicated a significantly lower QOL with or without the overlap population. This effect was absent in the patients with cardiac cachexia even after combining with the overlap group.

HF is not the only chronic disease to induce sarcopenia. Many other chronic disorders are reported to involve muscle tissue. Foley et al. (2007) reported a prevalence of 31.7% for sarcopenia among CKD patients; they also found a lower likelihood of developing sarcopenia in physically active CKD patients. In addition, diabetic patients were found to have a three times higher risk of developing sarcopenia than the average population (Kim et al. 2010). Kim et al. showed a prevalence of 15.7% for sarcopenia among their diabetic patients. In 2015, Jones et al. studied 622 stable COPD patients with 14.5% prevalence for sarcopenia. Sarcopenic COPD patients in this study were demonstrated to have lower exercise capacity (Jones et al. 2015).

Cachexia was first acknowledged as a prognostic risk factor in HF patients in 1997. Anker et al. showed a prevalence of 16% for cachexia in their HF patients. They demonstrated a significantly higher mortality rate in cachectic HF patients at 18 months of follow-up *vs.* the non-cachectic control group. Furthermore, cachectic HF patients showed significantly lower values for peakVO_2. However, muscle strength and QOL were not concretely assessed in this study. The prevalence of cachexia of 19% in our analysis was similar to Anker at al. results. In our study, all groups with wasting showed lower peakVO_2 *vs.* the control group. We did not assess the long time survival of the patients, though.

In a very recent prospective study with 268 patients, von Haehling et al. showed muscle wasting to be an independent predictor of death among ambulatory HF patients (von

Haehling et al. 2020). This effect was discussed to be more pronounced in HFrEF than HFpEF patients (von Haehling et al. 2020). A lower prevalence of muscle wasting in their study (17.5%) could be due to the inclusion female patients. This study confirmed that not only cachexia but also sarcopenia has a prognostic impact on chronic HF.

Muscle wasting was shown to be present in 47.3% of HF patients with non-ischemic dilated cardiomyopathy (Hajahmadi et al. 2017). Compared to our analysis, a higher prevalence of muscle wasting in the Hajahmadi et al. study could be due to the inclusion of only HFrEF patients. Since dilated cardiomyopathy is a genetically determined disease, it cannot be excluded that some of these patients had a muscular disease such as myositis. Hajahmadi et al. reported a significantly shorter distance walked in 6MWT among HF patients with muscle wasting (Hajahmadi et al. 2017); this was in agreement with our study. HF patients with sarcopenia in our analysis also indicated weaker results in 6MWT. However, this effect was not observed among cachectic HF patients.

In the Studies of Left Ventricular Dysfunction (SOLVD) with 1929 HF patients, Anker et al. (2003) discussed a weight loss ≥ 6% as the strongest predictor of impaired survival. Other cut-off values for weight loss, including ≥ 5.0%, ≥ 7.5%, ≥ 10.0%, and ≥ 15.0%, did not show the same prognostic significance (Anker et al. 2003). Based on these results, we took the 6% cut-off to define cachexia among our HF patients. The prevalence of cachexia in Anker et al. study was 36%. A higher prevalence of cachexia in Anker et al. data could result from the more extended follow-up (35±13 months). The time window to define cachexia in our study was 12 months.

Fülster et al. (2013), with the same SICA-HF database, studied HF patients' body composition with a DXA scanner. They found a prevalence of 19.5 % for muscle wasting among their 200 ambulatory HF patients. Similar to our analysis, they showed reduced exercise capacity and muscle strength among HF patients with muscle wasting (Fülester et al. 2013). However, they did not address the cardiac cachexia and its overlap with muscle wasting. Furthermore, in this study, the changes in the QOL were not discussed.

Later in another prospective analysis with 117 HF patients, Bekfani et al. (2016) showed a prevalence of 19.7% for muscle wasting among HF patients with HFpEF. This study confirmed that HFpEF patients with muscle wasting tend to have significantly lower exercise capacity, muscle strength, and QOL. Bekfani et al. highlighted the importance of early diagnosis of muscle wasting in HFpEF patients. In our analysis, we included both HFrEF and HFpEF patients. However, we separated the cachectic and sarcopenic patients and

compared their impact on different aspects of functional capacity, muscle strength, and QOL.

In another study, in the framework of SICA-HF with 228 HF patients, Dos Santos et al. (2016) discussed the impact of endothelial dysfunction on functional capacity among HF patients with sarcopenia. They discussed a blunted vasodilatation in sarcopenic patients, which was associated with lower functional capacity (Dos Santos et al. 2016). This study implemented the same database as our analysis with the inclusion of female patients, but they did not assess the SPPB-score, muscle strength, or QOL. Furthermore, they did not address cachectic patients and the potential overlap population separately.

In their cross-sectional study, Canteri et al. (2019) reported a prevalence of 30.4% for sarcopenia among HFrEF patients. The higher prevalence of sarcopenia in this study could be emerged due to the exclusion of HFpEF patients. Furthermore, a smaller study population and different anthropometric profiles could contribute to this difference. In concordance with our analysis, they showed lower handgrip strength in men with sarcopenia *vs.* the control group. However, the same effect could not be determined in female patients with sarcopenia.

Lower AMSI was recently discussed as a prognostic factor among patients with ST-Elevation Myocardial Infarction (STEMI, Sato et al. 2020). Sato et al. demonstrated a lower ASMI to be independently associated with a higher risk of primary composite events. Similar to our study, they found that the patients with lower ASMI were older and had lower BMI and hemoglobin levels (Sato et al. 2020). In contrast to our analysis, Sato et al. used a lower cut-off for ASMI than the cut-off determined by the Asian Working Group for Sarcopenia (AWGS, ≤ 6.64 kg/m^2 for men and ≤ 5.06 kg/m^2 for women).

A cross-sectional study with 155 HF patients Nakano et al. (2020) indicated an association between loop diuretics therapy and smaller thigh circumference. They implemented tight circumference instead of DXA to define muscle loss. Arm or thigh circumference could be an acceptable or practical reflection of muscle mass, but they are known to have lower accuracy than DXA. In our analysis, 59% of patients were treated with a loop or thiazide diuretic. No significant difference in the application of loop diuretics was found, though (Table 3).

Clark AL et al. (2017), in a prospective study with 2289 patients (COPERNICUS trial), reported a partial reversal of cachexia in severe HF under therapy with carvedilol. In concordance to our research, they used the same 6% cut-off to define cardiac cachexia. The carvedilol group showed a lower likelihood of developing a significant weight loss

(>6%) *vs.* the placebo group. Their study did not mainly address sarcopenia or exercise capacity.

In a randomized trial with 237 patients, Nipp et al. (2017) showed lower QOL and a higher risk of depression among sarcopenic patients with advanced lung cancer. Nipp et al. used the skeletal muscle cross-sectional area (CSA) at the level of the third lumbar vertebrae, measured during an abdominal CT scan, to define sarcopenia (< 55 cm^2 for men and < 39 cm^2 for women, Fearon et al. 2011). The prevalence of sarcopenia among their cancer population was 55.3% (Nipp et al. 2017). A very high prevalence of sarcopenia, particularly in lung cancer patients, is well known (Buentzel et al. 2019). Assessment of sarcopenia in follow-ups CT scans is applicable among cancer patients. However, due to high radiation exposure and cost, a CT scan cannot be a suitable option for HF patients.

Another ongoing debate related to sarcopenia is frailty. Frailty is defined as an increased age-dependent vulnerability (Bielecka-Dabrowa et al. 2020). Due to higher rates of falls, institutionalization, and hospitalization, frailty is associated with poor prognosis and higher mortality rates (Bielecka-Dabrowa et al. 2020, Fried et al. 2001). Frailty is discussed to be a result of loss in muscle mass and bone mineral density (BMD, Bielecka-Dabrowa et al. 2020). According to ESC, frailty in HF is defined as a multidimensional dynamic state, independent of age, which makes the HF patient more vulnerable to stressors (Vitale et al. 2019, Bielecka-Dabrowa et al. 2020). Frailty is shown to be associated with a 92% higher risk for emergency department visits and a 65% higher risk for hospitalization (McNallan et al. 2013). Cachexia could involve different body compartments, including fat-free mass, fat mass, and bone mass (Bielecka-Dabrowa et al. 2020). In our analysis, we did not address the frailty or changes in BMD, but cachectic HF patients showed lower exercise tolerance without a significant loss in muscle mass.

Muscle wasting is expected to occur among healthy elderly subjects as a result of the aging process (Bielecka-Dabrowa et al. 2020). However, chronic diseases like HF can contribute to the process of muscle loss, which can explain the higher prevalence of sarcopenia in HFrEF (19.5%, Fülster et al. 2013) and HFpEF (19.7%, Bekfani et al. 2016). The higher prevalence of sarcopenia in chronic disease could be due to inflammatory responses. IL-6 has been viewed primarily as an inflammatory factor (Bielecka-Dabrowa et al. 2020). IL-6 promotes glucose uptake and fatty acid oxidation locally in the muscle, increases fatty acid release from adipocytes, and stimulates the secretion of glucagon-like peptide-1 (GLP-1, Bielecka-Dabrowa et al. 2020). In our analysis, IL-6 levels were significantly higher in the

overlap group *vs.* the control group ($p < 0.05$, Table 3). Other inflammatory parameters like IL-1β or TNF didn't show the same significance.

Our study highlights the impacts of muscle wasting on functional capacity and QOL among HF patients. Cachexia has demonstrated some negative influence on functional performance, but this effect was less significant. Sarcopenic patients can lose lean muscle even without a substantial weight loss. On the other hand, cachexia can occur due to loss in skeletal muscle, bone, or adipose tissue. Early stages of sarcopenia with mitochondrial dysfunction, fiber transformation, and fatty infiltration could manifest without an associated weight loss (von Haehling et al. 2017b). The beginning impacts of sarcopenia could emerge without any relevant changes in patients' BMI.

On the other side of the spectrum, obesity is a known independent risk factor for chronic HF (Horwich et al. 2018). During the last decade, obesity has been shown to have a paradoxical significant survival benefit in chronic HF (Simonenko 2019, Anker and von Haehling 2011). Due to higher BMI, obese patients may experience more limitations in their exercise tolerance and QOL, encouraging them to present themselves earlier for therapy. It is assumed that obese patients have a lower circulatory BNP and an attenuated response to the renin-angiotensin-aldosterone system (Horwich et al. 2018, Lavie et al. 2009, Mehra et al. 2004). These factors contribute to maintain higher blood pressures and preserve renal circulation (Horwich et al. 2018). Under these circumstances, cardioprotective medications such as beta-blockers, ACE-inhibitors, and neprilysin inhibitors could be applied in higher doses (Horwich et al. 2018). The latest ESC guidelines for HF does not include a weight loss program for patients with non-morbid obesity (BMI < 35 kg/m^2, ESC 2016). The obesity paradox underscores this assumption that BMI cannot adequately represent the body composition among HF patients.

Muscle wasting in HF has profound impacts on patients' exercise tolerance and QOL. Sarcopenic patients tend to be physically dependent on others in later life (Dos Santos et al. 2017). In the latest ESC guidelines, sarcopenia is acknowledged as a co-morbidity of HF. Early diagnosis and management of both sarcopenia and cachexia in HF are modulatory. As mentioned before, no particular pharmacologic therapies for sarcopenia have been approved yet (ESC 2016).

Being aware of the high prevalence of HFpEF among women, SICA-HF originally included 20.5% female patients. The main limitation of our analysis was the low prevalence of females with sarcopenia and cachexia. For example, no female patient was present in our overlap group, so that we excluded females from our analysis. It has been long established that

testosterone is a potent anabolic factor for maintaining muscle mass (Anderson et al. 2017). Testosterone promotes protein synthesis and muscular regeneration, which is abundant in healthy young men (Anderson et al. 2017). During aging or other chronic disorders, testosterone deficiency leads to a more robust catabolic response in men than women (Anderson et al. 2017). On the other hand, estrogens may have a protective effect on preserving muscle mass and function due to anti-inflammatory and anti-catabolic effects (Anderson et al. 2017). These changes could explain the smaller population of females with muscle wasting in our analysis. A prospective study among women with sarcopenic HF is currently underway.

Another limitation of our analysis was the small number of patients in the overlap group. We assume this problem to be due to an extra layer of grouping. We tried to overcome this limitation through our alternative analyses, which showed significantly lower results in the sarcopenic groups with or without the overlap population. Future studies needed to shed more light on this subtype of wasting.

4.1 Conclusions

Sarcopenia and cachexia in HF are shown to be associated with higher morbidity and mortality (Anker et al. 1997, von Haehling et al. 2020). This study aimed to compare the impact of sarcopenia, cachexia, and their potential overlap on exercise tolerance and QOL among HF patients.

In our study cohort, the overlap group showed the most significant lower functional performance and QOL. The sarcopenic HF group also presented similarly lower results in most of the functional tests, including CPET, 6MWT distance, SPPB, muscle strength, and EQ-5D index score. This effect remained constant after joining the overlap group into either the cachectic-HF or sarcopenic-HF. The cachectic HF group demonstrated some weaker results in peakVO_2 and quadriceps strength. However, lower QOL was observed only in groups with characteristics of sarcopenia.

Weight loss, as used to define cachexia, cannot comprehensively represent the body composition among HF patients. Sarcopenic patients, especially at the beginning of the disease, due to fatty tissue infiltration and inflammatory changes, may not show any measurable weight loss. Besides, due to other factors, e.g., peripheral edema, diuretic therapy, and obesity paradox, a simple scale cannot be reliable for evaluating HF patients. Early assessment of body composition with a DXA scanner should be implemented in the management of HF patients.

Our analysis could be helpful, particularly for the devolvement of therapeutic pathways to improve exercise tolerance and QOL in chronic HF. Due to prognostic significance, both sarcopenia and cachexia should be targeted to develop future treatments. However, sarcopenia might be the priority in this regard. Future clinical trials need to address the impacts of gender differences on functional performance and QOL among HF patients.

5 Abstract

Muscle wasting is acknowledged as a co-morbidity of heart failure (HF) and is associated with poor prognosis (ESC 2016). Cardiac cachexia is known to cause reduced functional capacity, more frequent hospitalization, and decreased survival rate (ESC 2016). This study aimed to compare the impacts of sarcopenia, cachexia, and their overlap on exercise tolerance and quality of life (QOL) in chronic HF patients.

We included retrospectively 207 outpatients with chronic HF into a cross-sectional study based on the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) database. Body composition was measured using dual-energy X-ray absorptiometry (DXA). Functional performance was assessed with peak oxygen uptake ($peakVO_2$), 6-minute-walk-test (6MWT), and short physical performance battery (SPPB) test. The handgrip and quadriceps strength were measured using isokinetic dynamometry. Quality of life (QOL) was evaluated using the EuroQol-5-Dimension (EQ-5D) questionnaire to calculate the EQ-5D index score.

Sarcopenia was present in 21.3% of our HF patients. In this context, 14.5% fulfilled sarcopenia's definition without associated cachexia (sarcopenic HF group). 12.1% presented with cachexia without concomitant sarcopenia (cachectic HF group). Furthermore, 6.8% of patients demonstrated the characteristics of both cachexia and sarcopenia (overlap group).

The lowest results for functional capacity, muscle strength, and QOL were observed in patients with sarcopenia. Both of the overlap and sarcopenic HF groups showed the lowest values for muscle strength, 6MWT distance, $peakVO_2$, SPPB score, and EQ-5D index score *vs.* control group (all $p < 0.05$). The overlap group showed the weakest quadriceps strength *vs.* all other groups ($p < 0.05$). We found significantly lower results for $peakVO_2$ and quadriceps strength among the cachectic HF group *vs.* the control group, but this effect was not constant in other functional tests. The cachectic HF could not demonstrate significantly lower QOL indices.

Male HF patients with sarcopenia seem to have significantly lower functional performance and QOL. These effects remain constant with/or without associated cachexia. Our study highlights the importance of early screening for sarcopenia among HF patients. In this regard, BMI cannot be a reliable representative of patients' body composition.

6 References:

Abellan van Kan G (2009): Epidemiology and consequences of sarcopenia. J Nutr Health Aging 13, 708-712

Alchin DR (2014): Sarcopenia: describing rather than defining a condition. J Cachexia Sarcopenia Muscle 5, 265-268

Anderson LJ, Liu H, Garcia JM (2017): Sex Differences in Muscle Wasting. Adv Exp Med Biol 1043, 153-197

Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ (1997): Wasting as an independent risk factor for mortality in chronic heart failure. Lancet 349, 1050-1053

Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S (2003): Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 361, 1077-1083.

Anker SD, von Haehling S (2011): The obesity paradox in heart failure: accepting reality and making rational decisions. Clin Pharmacol Ther 90, 188-190

Argilés JM, Busquets S, Stemmler B, López-Soriano FJ (2014): Cancer cachexia: understanding the molecular basis. Nat Rev Cancer 14, 754-762

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002): ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166, 111-117

Bauer J, Morley JE, Schols AMWJ, Ferrucci L, Cruz-Jentoft AJ, Dent E, Baracos VE, Crawford JA, Doehner W, Anker SD (2019): Sarcopenia: A Time for Action. An SCWD Position Paper. J Cachexia Sarcopenia Muscle 10, 956-961

Bekfani T, Pellicori P, Morris DA, Ebner N, Valentova M, Steinbeck L, Wachter R, Elsner S, Sliziuk V, Schefold JC et al. (2016): Sarcopenia in patients with heart failure with preserved ejection fraction: Impact on muscle strength, exercise capacity and quality of life. Int J Cardiol 222, 41-46

Bielecka-Dabrowa A, Ebner N, Dos Santos MR, Ishida J, Hasenfuss G, von Haehling S (2020): Cachexia, muscle wasting, and frailty in cardiovascular disease. Eur J Heart Fail (in print)

Bredella MA, Ghomi RH, Thomas BJ, Torriani M, Brick DJ, Gerweck AV, Misra M, Klibanski A, Miller KK (2010): Comparison of DXA and CT in the assessment of body composition in premenopausal women with obesity and anorexia nervosa. Obesity (Silver Spring) 18, 2227-2233

Bruce RA, Blackmon JR, Jones JW, Strait G (1963): Exercise testing in normal adult subjects and cardiac patients. Pediatrics 32, 742-756

Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, Maggi S, Dennison E, Al-Daghri NM, Allepaerts S et al. (2018): Pitfalls in the measurement of muscle mass: a need for a reference standard. J Cachexia Sarcopenia Muscle 9, 269-278

Buentzel J, Heinz J, Bleckmann A, Bauer C, Röver C, Bohnenberger H, Saha S, Hinterthaner M, Baraki H, Kutschka I et al. (2019): Sarcopenia as Prognostic Factor in Lung Cancer Patients: A Systematic Review and Meta-analysis. Anticancer Res 39, 4603-4612

Cahalin LP, Mathier MA, Semigran MJ, Dec GW, Di Salvo TG (1996): The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest 110, 325-332

Canteri AL, Gusmon LB, Zanini AC, Nagano FE, Rabito EI, Petterle RR, Jonasson TH, Boguszewski CL, Borba VZC (2019): Sarcopenia in heart failure with reduced ejection fraction. Am J Cardiovasc Dis 15, 116-126

Cawthon PM, Fox KM, Gandra SR et al (2009): Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? J Am Geriatr Soc 57, 1411-1419

Chan OY, van Houwelingen AH, Gussekloo J, Blom JW, den Elzen WP (2014): Comparison of quadriceps strength and handgrip strength in their association with health outcomes in older adults in primary care. Age (Dordr) 36, 9714

Clark RV, Walker AC , Miller RR , O'Connor-Semmes RL , Ravussin E, Cefalu WT (2017): Creatine (Methyl-D 3) Dilution in Urine for Estimation of Total Body Skeletal Muscle Mass: Accuracy and Variability vs. MRI and DXA. J Appl Physiol 124, 1-9

Clark AL, Coats AJS, Krum H, Katus HA, Mohacsi P, Salekin D, Schultz MK, Packer M, Anker SD (2017): Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic heart failure: results from the COPERNICUS trial. J Cachexia Sarcopenia Muscle 8, 549-556

Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM (2010): Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 39, 412-423

Dos Santos L, Cyrino ES, Antunes M, Santos DA, Sardinha LB (2017): Sarcopenia and physical independence in older adults: the independent and synergic role of muscle mass and muscle function. J Cachexia Sarcopenia Muscle 8, 245-250

Dos Santos MR, Saitoh M, Ebner N, Valentova M, Konishi M, Ishida J, Emami A, Springer J, Sandek A, Doehner W et al. (2016): Sarcopenia and Endothelial Function in Patients With Chronic Heart Failure: Results From the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). J Am Med Dir Assoc 18, 240-245

Emami A, Saitoh M, Valentova M, Sandek A, Evertz R, Ebner N, Loncar G, Springer J, Doehner W, Lainscak M et al. (2018): Comparison of sarcopenia and cachexia in men with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). Eur J Heart Fail 20, 1580-1587

EuroQol Group (1990): EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 16, 199-208

Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G et al. (2011): Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12, 489-495

Foley RN, Wang C, Ishani A, Collins AJ, Murray AM (2007): Kidney function and sarcopenia in the United States general population: NHANES III. Am J Nephrol 27, 279-286

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G et al. (2001): Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56, 146-156

Fülster S, Tacke M, Sandek A, Ebner N, Tschöpe C, Doehner W, Anker SD, von Haehling S (2013): Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). Eur Heart J 34, 512-519

Gallagher AM, Lucas R, Cowie MR (2019): Assessing health-related quality of life in heart failure patients attending an outpatient clinic: a pragmatic approach. ESC Heart Fail 6, 3-9

Gallagher D, Visser M, Meersman R E De, Sepúlveda D, Baumgartner RN, Pierson RN, Harris T, Heymsfield SB (1997): Appendicularskeletalmusclemass: effects of age, gender, and ethnicity. J Appl Physiol 83, 229-239

Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB (1994): A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 49, 85- 94

Hairi NN, Cumming RG, Naganathan V, Handelsman DJ, Le Couteur DG, Creasey H, Waite LM, Seibel MJ, Sambrook PN (2010): Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. J Am Geriatr Soc 58, 2055-2062

Hajahmadi M, Shemshadi S, Khalilipur E, Amin A, Taghavi S, Maleki M, Malek H, Naderi N (2017): Muscle wasting in young patients with dilated cardiomyopathy. J Cachexia Sarcopenia Muscle 8, 542- 548

Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM (2013): Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 6, 606-619

Ishida J, Saitoh M, Ebner N, Springer J, Anker SD, von Haehling S (2019): Growth hormone secretagogues: history, mechanism of action and clinical development. JCSM Rapid Communications 3, 25-37

Januzzi JL, Mann DL: Approach to the Patient with Heart Failure. In: Libby P, Zipes DP, Bonow RO, Mann DL, Tomaselli GF, Bhatt D (Hrsg.): Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 11th edition. Elsevier. Philadelphia 2018, 403-417

Javaheri S, Caref EB, Chen E, Tong KB, Abraham WT (2011): Sleep apnea testing and outcomes in a large cohort of Medicare beneficiaries with newly diagnosed heart failure. Am J Respir Crit Care Med 183, 539-546

Jones SE, Maddocks M, Kon SS, Canavan JL, Nolan CM, Clark AL, Polkey MI, Man WD (2015): Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. Thorax 70, 213-218

Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W, Haass M (2002): Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart 87, 235-241

Kaminsky LA, Tuttle MS (2015): Functional assessment of heart failure patients. Heart Fail Clin 11, 29-36

Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, Seo JA, Kim SG, Kim NH, Baik SH (2010): Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Care 33, 1497-1499

Kotler DP, Tierney AR, Wang J, Pierson RN Jr (1989): Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. Am J Clin Nutr 50, 444-447.

Lainscak M, Anker SD (2015): Heart failure, chronic obstructive pulmonary disease, and asthma: numbers, facts, and challenges. ESC Heart Fail 2, 103-107

Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T et al. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 16, 233-270

Laukkanen P, Heikkinen E, Kauppinen M (1995): Muscle strength and mobility as predictors of survival in 75-84-year-old people. Age Ageing 24, 468-473

Lavie CJ, Milani RV, Ventura HO (2009): Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 53, 1925-1932

Lewis ME, Newall C, Townend JN, Hill SL, Bonser RS (2001): Incremental shuttle walk test in the assessment of patients for heart transplantation. Heart 86, 183-187

Lucas C, Stevenson LW, Johnson W, Hartley H, Hamilton MA, Walden J, Lem V, Eagen-Bengsten E (1999): The 6-min walk and peak oxygen consumption in advanced heart failure: aerobic capacity and survival. Am Heart J 138, 618-624

Maden-Wilkinson TM, Degens H, Jones DA, McPhee JS (2013): Comparison of MRI and DXA to measure muscle size and age-related atrophy in thigh muscles. J Musculoskelet Neuronal Interact 13, 320-328

Mann DL, Chakinala M: Heart Failure: Pathophysiology and Diagnosis. In: Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J (Hrsg.): Harrison's Principles of Internal Medicine. 20th edition; McGraw-Hill Education/Medical, New York 2018, 1763-1769

Malhotra R, Bakken K, D'Elia E, Lewis GD (2016): Cardiopulmonary Exercise Testing in Heart Failure. JACC Heart Fail 4, 607-616

Mazurek JA, Jessup M (2017): Understanding Heart Failure. Heart Fail Clin 1, 1-19

Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC, Frohlich ED (2004): Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 43, 1590-1595

Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, Cederholm T, Coats AJ, Cummings SR, Evans WJ (2011): Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc 12, 403-409

Nakano I, Tsuda M, Kinugawa S, Fukushima A, Kakutani N, Takada S, Yokota T (2020): Loop diuretic use is associated with skeletal muscle wasting in patients with heart failure. J Cardiol 76, 109-114

National Kidney Foundation (2002): K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39, 1-266

Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, Tylavsky FA, Rubin SM, Harris TB (2006): Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 61, 72-77

Okoshi MP, Romeiro FG, Paiva SA, Okoshi K (2013): Heart failure-induced cachexia. Arq. Bras. Cardiol 100, 476-482

Pataky Z, Armand S, Müller-Pinget S, Golay A, Allet L (2014): Effects of obesity on functional capacity. Obesity 22, 56-62

Payne-Emerson H, Lennie TA (2008): Nutritional considerations in heart failure. Nurs Clin North Am 43, 117-132

Piepoli MF, Davos C, Francis DP, Coats AJ; ExTraMATCH Collaborative (2004): Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 328, 189-196

Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA (2016): 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37, 2129-2200

Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V et al. (2015): Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 36, 657-668

Ramos-Barbón D, Fitchett D, Gibbons WJ, Latter DA, Levy RD (1999): Maximal exercise testing for the selection of heart transplantation candidates: limitation of peak oxygen consumption. Chest 115, 410-417

Rantanen T, Era P, Heikkinen E (1994): Maximal isometric strength and mobility among 75-year-old men and women. Age Ageing 23, 132-137

Rosenberg, I. H (2011): Sarcopenia: origins and clinical relevance. Clin Geriatr Med 27, 337-329

Roubenoff R, Heymsfield SB, Kehayias JJ, Cannon JG, Rosenberg IH. Cannon JG, Rosenberg IH (1997): Standardization of nomenclature of body composition in weight loss. Am J Clin Nutr 66, 192-196

Saitoh M, Ishida J, Ebner N, Anker SD, Springer J and von Haehling S (2017): Myostatin inhibitors as pharmacological treatment for muscle wasting and muscular dystrophy. JCSM Clinical Reports 2, 1-10

Sato R, Akiyama E, Konishi M, Matsuzawa Y, Suzuki H, Kawashima C, Kimura Y, Okada K, Maejima N, Iwahashi N et al. (2020): Decreased Appendicular Skeletal Muscle Mass is Associated with Poor Outcomes after ST-Segment Elevation Myocardial Infarction. J Atheroscler Thromb (in print)

Schefold JC, Lainscak M, Hodoscek LM, Blöchlinger S, Doehner W, von Haehling S (2015): Single baseline serum creatinine measurements predict mortality in critically ill patients hospitalized for acute heart failure. ESC Heart Fail 2, 122-128

Schneider H, Nienaber CA: Herzinsuffizienz. In: Arastéh K, Baenkler HW, Bieber C, Brandt R, Chatterjee TT (Hrsg.): Duale Reihe Innere Medizin. 4. Auflage; Thieme, Stuttgart 2018, 99-114

Simonenko M (2019): Obesity paradox in heart failure: A matter of debate. Eur J Prev Cardiol 26,1748-1750

Tanai E, Frantz S (2015): Pathophysiology of heart failure. Compr Physiol 6, 187-214

Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, Simonsick EM, Harris TB (2005): Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 60, 324-333

Vitale C, Jankowska E, Hill L, Piepoli M, Doehner W, Anker SD, Lainscak M, Jaarsma T, Ponikowski P, Rosano GMC et al. (2019): Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. Eur J Heart Fail 21, 1299-1305

von Haehling S, Garfias Macedo T, Valentova M, Anker MS, Ebner N, Bekfani T, Haarmann H, Schefold JC, Lainscak M, Cleland JGF et al. (2020): Muscle wasting as an independent predictor of survival in patients with chronic heart failure. J Cachexia Sarcopenia Muscle 11, 1242-1249

von Haehling S (2017a): Co-morbidities in heart failure beginning to sprout and no end in sight? Eur J Heart Fail 19, 1566-1568

von Haehling S, Ebner N, Dos Santos MR, Springer J, Anker SD (2017b): Muscle wasting and cachexia in heart failure: mechanisms and therapies. Nat Rev Cardiol 14, 323-341

von Haehling S, Lainscak M, Doehner W, Ponikowski P, Rosano G, Jordan J, Rozentryt P, Rauchhaus M, Karpov R, Tkachuk V et al. (2010a): Diabetes mellitus, cachexia, and obesity in heart failure: rationale and design of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). J Cachexia Sarcopenia Muscle 1, 187-194

Yin J, Lu X, Qian Z, Weiting X, Zhou X (2019): New insights into the pathogenesis and treatment of sarcopenia in chronic heart failure. Theranostics 9, 4019-4029

Danksagung

Mein Dank gilt einer großen Zahl von Menschen, ohne die diese Arbeit nicht zustande gekommen wäre. Herrn Prof. Dr. Gerd Hasenfuß danke ich sehr herzlich für die Möglichkeit, diese Arbeit in seiner Klinik zu verfassen. Ganz besonders danke ich Prof. Dr. Stephan von Haehling für die Überlassung des Themas dieser Arbeit und die ausgezeichneten Möglichkeiten, es zu bearbeiten, ohne seine Rückendeckung und unsere vielen, immer wieder auch kritischen Diskussionen wäre diese Arbeit nicht möglich gewesen. Herrn Dr. Jochen Springer ebenso wie Herrn Dr. Masakazu Saito gilt mein besonderer Dank, da ihre Hilfe meine klinische und wissenschaftliche Ausbildung entscheidend mitgeprägt hat.

Viele andere haben unmittelbar zum Entstehen dieser Arbeit beigetragen, indem sie die Studien, die ihren Kern darstellen, mitgestaltet und geprägt haben. Dies gilt insbesondere für Frau Dr. Miroslava Valentova, Dr. Anja Sandek sowie Herrn Dr. Marcelo Rodrigues dos Santos. Daneben gilt mein herzlichen Dank Frau Dr. Tania Garfias-Macedo, die unmittelbar zum Entstehen der Projekte dieser Arbeit beigetragen hat.

Den Mitarbeitern unserer Arbeitsgruppe danke ich für die stets angenehme Atmosphäre und die konstruktive Zusammenarbeit, namentlich Frau Christine Diehl, Bettina Steinhop sowie Anja Janssen.